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ORIGINAL PAPER

Mismatch Negativity and P3a in Adolescents and Young Adults with Autism Spectrum Disorders: Behavioral Correlates and Clinical Implications

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Abstract
In a sample of 37 adolescents and young adults with autism spectrum disorder (ASD) and 35 typically-developing controls (TDC), we investigated sensory symptoms by clinical measures, and Mismatch Negativity and P3a component at Fz with the frequency and duration oddball paradigms of event-related potentials. Results showed that compared to TDC, ASD participants reported more sensory symptoms, and presented a shorter P3a peak latency in the duration paradigm, which was correlated with more social awareness deficits. In the frequency paradigm, P3a parameters were correlated with sensation avoiding and attention characteristics of ASD. Our findings suggest that sensory abnormality in ASD may extend into adolescence and young adulthood. P3a latency might be a potential neurophysiological marker for ASD.

Keywords Autism spectrum · Event-related potentials · Mismatch negativity · P3a · Correlates

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by qualitative impairment in social reciprocity and communication and restricted repetitive behavior or interest (American Psychiatric Association 2013). The new diagnostic criteria for ASD proposed in the DSM-5 include sensory profiles as core features and specifically describes 'hypo- and hyper-reactivity to sensory input, unusual interests in sensory aspects of the environment, and restricted and repetitive interests in sensory based activities' (American Psychiatric Association 2013). To facilitate the diagnostic procedure of ASD, comprehensive assessments of sensory symptoms combining both subjective and objective measurements are clinically relevant in any age group of ASD (Ausderau et al. 2013).

A systemic review of the literature indicates that the prevalence of sensory symptoms is up to 90% in children with autism (Baker et al. 2008; Baranek et al. 2006). Among the sensory modalities, auditory perceptual disturbances were most frequently involved, with a prevalence of 16–100% for auditory hypersensitivity (Gomes et al. 2008), 18–63% for hyperacusis (Khalfa et al. 2004; Rosenhall et al. 1999) and paradoxical responses to sounds (Baranek et al. 2006). Despite a high prevalence in children with ASD, few studies have investigated the sensory symptoms in adults with this disorder (Crane et al. 2009; Tavassoli et al. 2013). Available data revealed that the unusual sensory symptoms in ASD seem to extend across the lifespan. The age trends in sensory over-responsiveness have been documented in both ASD and controls, showing that the older participants display fewer differences than younger participants (Crane et al. 2009). However, adults with ASD may still show sensory symptoms in the most extreme end of the Sensation Seeking, Low Registration, Sensation Avoiding, and Sensory Sensitivity subscales of the Adolescent/Adult Sensory Profile (Crane

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et al. 2009). These data rated on the questionnaire reflect the subjective sensory experience of ASD individuals.

To characterize the sensory features of ASD objectively, researchers used the event-related potential (ERP) to assess the brain's electrical activity in response to the auditory stimulation (Orekhova and Stroganova 2014). An analytic review concluded that the impairment in autism likely exists in different levels of auditory processing, and suggested the application of ERPs to detect neurophysiological endophenotype for quantitative genetic studies (Jeste and Nelson 2009). Among the ERP paradigms, mismatch negativity (MMN) and P3a (Escera et al. 2000) involve pre-attentive change detection and involuntary orientation to the changes in a sequence of otherwise repetitive stimuli which subjects do not need to pay attention to. MMN is automatically generated whenever there is a mismatch between the neuronal model of the physical features of the standard stimulus and the deviant stimulus (Näätänen et al. 2012), reflecting cortical discrimination of sound changes. P3a is the positive deflection automatically arising after the MMN waveform and has a frontal/central maximum amplitude distribution (Polich 2007; Polich and Criado 2006), reflecting involuntary orienting to attention-catching changes.

In MMN studies, shorter latency and larger amplitude to the changes of frequency have been reported in youth with ASD (age range 5–15 years) compared to age-matched typically-developing (TD) youth (Ferri et al. 2003; Gomot et al. 2002, 2006, 2011). These findings suggest that youth with ASD were able to discriminate frequency change equally well as the controls (Ceponiene et al. 2003) and that their brain was even more sensitive (by showing earlier and larger MMN waves) towards the frequency change than the controls (Ferri et al. 2003; Gomot et al. 2002; Lepistö et al. 2005; Yu et al. 2015). By contrast, some studies showed that children with autism had diminished MMN amplitude for the duration (Lepistö et al. 2005) and consonant changes (Kuhl et al. 2005; Vlaskamp et al. 2017) suggesting deficits in discriminating those deviant stimuli (Dunn et al. 2008; Lepistö et al. 2006); whereas, still others reported normal MMN amplitude (Ceponiene et al. 2003). Both normal (Ceponiene et al. 2003; Lepistö et al. 2006, 2007) and longer (Abdeltawwab and Baz 2015; Jansson-Verkasalo et al. 2003; Seri et al. 1999) MMN latencies have also been reported, suggesting no consistent results across studies yet.

In P3a studies, the P3a response to highly attention-catching novel sounds was enhanced (by showing larger P3a amplitude) in children with autism (Ferri et al. 2003; Gomot et al. 2011) but the findings were inconsistent in adolescents with autism (Courchesne et al. 1984) and adults with ASD (Iwanami et al. 2014; Karhson and Golob 2016). These studies reported either a larger P3a amplitude in adults with ASD (Iwanami et al. 2014) or no difference compared to controls (Courchesne et al. 1984; Karhson and Golob 2016). When elicited by the changes in speech or non-speech sounds, the P3a appears to diminish in children with autism particularly for speech changes as opposed to non-speech changes (Ceponiene et al. 2003; Lepistö et al. 2005), suggesting deficits particularly in speech orienting (Lepistö et al. 2005).

Although ERP abnormalities have been proposed to be a candidate endophenotype for ASD (Gomot et al. 2011), such a finding needs further validation because of small number of ASD participants (Cui et al. 2016) in most existing studies (ranging from 5 to 28 subjects) (Cui et al. 2016; Kujala et al. 2007; Lepistö et al. 2007). The question about whether ERP abnormalities noted in children with ASD persist into adulthood waits to be answered. Studies have shown that functional connectivity of the brain was an important neural correlate of ERP (Cardenas et al. 2005; Choi et al. 2013; Hsiao et al. 2010). Evidence supports an altered developmental trajectory of brain connectivity in ASD individuals, with widespread hyperconnectivity in the childhood (Di Martino et al. 2011; Malaia et al. 2016; Supekar et al. 2013) but underconnectivity (Assaf et al. 2010; Gotts et al. 2012; Kennedy and Courchesne 2008; Monk et al. 2009; von dem Hagen et al. 2013) with local over-connectivity in the adulthood (Peters et al. 2013). Brain hyperconnectivity in the childhood was related to the severity of autistic symptoms such that children with greater connectivity exhibited more severe social impairment (Supekar et al. 2013). Brain hyperconnectivity may result in isolation of neural systems and a limitation of flexible resource allocation, thus contributing to some core behavioral characteristics of ASD, such as a need for sameness (Supekar et al. 2013). Such hyperconnectivity might also contribute to "islets" of spared ability in autism, as have been described in the domains of visual search (Keehn et al. 2013) and mathematics (Baron-Cohen et al. 2007), implying its role in sensory and cognitive processing. Whether MMN and P3a, reflecting on novelty discrimination and attention orienting, also change with age, like the normalization of brain hyperconnectivity during neuromaturation, remains to be investigated. To date, there are few ERP studies in adolescence and adulthood, and the results are controversial. If an ERP parameter changes with age, it may not be appropriate to serve as a stable marker of neurophyisological endophenotype for ASD.

The clinical correlates of these ERP responses are largely unknown (Cui et al. 2016). MMN abnormalities have been found to be more prevalent in children with ASD who displayed higher resistance to change (Gomot et al. 2011), reflected basic abnormalities in the processing of sensory information especially in the automatic processing of changing stimuli (Gomot et al. 2011). There is a lack of data that test the relationship between P3a abnormalities and abnormal behaviors in patients with ASD to date. A recent meta-analysis suggested the need of further exploration of the P3a along with core behavioral symptoms of ASD (Cui et al.

2016). As MMN and P3a represent novelty detection and attention orienting, it is possible that these neurophysiological markers may index autistic traits that involve attention orientation, such as social awareness deficits, and attention to patterns and details. Children with ASD fail to orient their attention toward social stimuli when compared to TD controls (Dawson et al. 1998). How their attention characteristics relate to P3a physiological changes is of particular interest.

This study aimed to clarify ERP responses by testing both MMN and P3a in adolescents and young adults with ASD. Besides, we sought to examine how these electrophysiological markers relate to sensory symptoms and autistic symptoms in ASD. We used an ERP paradigm proposed by Rissling et al. (2012), which paradigm records MMN and P3a elicited by deviant duration (dMMN and dP3a) or frequency auditory stimuli (fMMN and fP3a). Our hypothesis is that adolescents and young adults with ASD may still have deviated ERP responses, which are correlated with sensory symptoms and clinical autistic symptoms relevant to attention, i.e., social awareness deficits, patterns preoccupation, and attention to details.

Methods

Participants and Procedure

The study was implemented after approved by Research Ethics Committee (ID: 200809066R) of the National Taiwan University Hospital. Written informed consents were obtained from the participants older than 18 years old and all the parents; participants younger than 18 years old provided written assent after detailed explanation of the objective and procedures of the study. We recruited 37 participants with clinical diagnosis either of autistic disorder (n = 11) or Asperger's disorder (n = 26) (ASD group, mean age ± standard deviation, SD, 21.0 ± 4.2 years old; range 15–30) and 35 TD controls (mean age ± SD, 20.5 ± 3.1 years old; range 15–27). The participants of the ASD group were referred from the outpatient clinics at the National Taiwan University Hospital, Taiwan. The clinical diagnoses of autistic disorder and Asperger's disorder were made by the first author (Chien) and the corresponding author (Gau), both were board-certified child psychiatrists, based on the DSM-IV diagnostic criteria. The clinical diagnoses of autistic disorder and Asperger's disorder were further confirmed by using the Chinese version of the Autism Diagnostic Interview-Revised [ADI-R, (Chien et al. 2010; Gau et al. 2011)].

The TD group was recruited by advertisement followed by a clinical assessment to exclude TD participants who had a diagnosis of any major psychiatric disorders. The age and sex distribution, and education years did not differ between the ASD and TD groups (Table 1). The ASD group had significantly lower IQ than the TD group on Wechsler Adult Intelligence Scale-Fourth Edition (Table 1). All the participants completed the diagnostic interview, the Wechsler Adult Intelligence Scale, ERP and clinical measures in the hospital.

Measures

The ADI-R (Lord et al. 1994) is a standardized, comprehensive, semi-structured, investigator-based interview of caregivers. It covers most developmental and behavioral aspects of ASD, including qualitative abnormalities in reciprocal social interaction, communication, and restricted, repetitive and stereotyped patterns of behaviors, for children with a mental age from 18 months into adulthood. The Chinese version of the ADI-R was approved by the World Psychological Association in 2007 and has been applied in several studies for the validation of ASD diagnosis (Chien et al. 2010; Gau et al. 2011).

The *Sensory Profile (SP)* (Dunn 1999) is a 60-item, self-report questionnaire to measure sensory/perception-related symptoms and behaviors (Brown et al. 2001). It covers six sensory modalities, including taste/smell, motion, visual, tactile, activity, and auditory sensation. The rating is based on 5-point Likert: '1' never (0%), '2' seldom (25%), '3' sometimes (50%), '4' frequently (75%), '5' always (100%). The scoring method was based on 4-dimension structure, i.e., Low Registration (15 items, e.g., do not notice when being greeted/touched), Sensation Seeking (15 items, e.g., like to add pepper/chili in food), Sensory Sensitivity (15 items, e.g., dislike being touched on the back), and Sensation Avoiding (15 items, e.g., escape from places with crowds or noises). The Chinese SP was proved reliable, with internal consistency 0.71–0.80 and test–retest reliability ICC 0.80–0.86 (Tseng and Chen 2009), and has been widely used in clinical research.

The *Social Responsiveness Scale (SRS)* (Constantino and Gruber 2005) is a 65-item self-rating scale that measures the severity of "autism spectrum" symptoms in natural social settings over the past 6 months. Items were rated on a 4-point Likert scale from '0' (not true) to '3' (almost always true). The SRS has been demonstrated to have good internal consistency, construct validity, inter-rater reliability, test–retest reliability, and discriminative validity in either clinical or normal population (Constantino and Gruber 2005). The cutoff threshold of the SRS total scores are 70 in males and 65 in females (Constantino and Gruber 2005; Constantino and Todd 2003). Factor analyses indicated a four-factor structure (Social Communication, Stereotyped Behaviors/Interest, Social Awareness, and Social Emotion) of the Chinese version with high internal consistency (Cronbach's alpha, .94–.95). Among the four subscales,

Table 1 The comparison of demographic data and clinical profiles (Social Responsiveness Scale subscores and Autism Spectrum Questionnaire subscores) between autism spectrum disorder (ASD) and typically-developing controls (TD)

	ASD (n = 37)		TD (n = 35)			
	Mean	SD	Mean	SD	Statistics	p
Male, N (%)	35 (94.6%)		32 (94.9%)		0.06	0.803
Age	21.0	4.2	20.5	3.1	−0.22	0.830
Education (years)	13.1	2.7	14.1	2.1	1.65	0.099
Full-scale IQ	99.3	18.8	110.6	10.5	−2.53	0.012
Verbal IQ	101.8	18.6	110.9	10.1	−1.92	0.055
Performance IQ	96.6	20.7	108.7	12.5	−2.79	0.005
Autism Diagnostic Interview-Revised						
Most severe at 4–5 years						
Social reciprocal interaction	18.1	7.4				
Communication: Verbal	7.5	3.7				
Nonverbal	14.2	5.3				
Repetitive/stereotyped behavior/interests	6.4	3.0				
Social Responsiveness Scale (T-score mean ± SD)						
Total scores	105.4 (80.6 ± 13.6)	24.9	44.6 (47.4 ± 8.48)	15.5	−6.98	<.0001
Social communication	45.7 (80.3 ± 15.5)	15.2	17.2 (51.3 ± 8.48)	8.3	−6.63	<.0001
Stereotyped behaviors/interest	23.5 (79.9 ± 13.1)	6.6	8.2 (49.4 ± 8.78)	4.4	−6.89	<.0001
Social awareness	21.4 (54.4 ± 6.91)	4.6	12.7 (41.4 ± 8.39)	5.6	−5.81	<.0001
Social emotion	14.7 (72.8 ± 12.5)	4.5	6.5 (50.2 ± 8.59)	3.1	−6.17	<.0001
Autism Spectrum Quotient						
Total score	101.5	11.0	75.7	9.4	6.51	<.0001
Socialness	38.3	6.3	26.3	5.3	5.98	<.0001
Mindreading	22.8	4.4	15.2	3.4	5.73	<.0001
Patterns preoccupation	11.2	3.1	10.0	2.4	1.58	0.115
Attention to details	11.4	2.1	9.9	1.7	3.12	0.002
Attention switching	17.8	2.8	14.3	2.2	4.76	<.0001

The comparisons were done by Wilcoxon two-sample test (two-sided, normal approximation). Sex distribution was compared by Fisher's exact test (two-sided). The total scores and subscores of Autism Diagnostic Interview-Revised, Social Responsiveness Scale, and Autism Spectrum Quotient were all raw scores. For Social Responsiveness Scale, the means and S.D. of T-scores were also provided

we selected Social Awareness subscore to test because P3a abnormality may suggest impaired social orienting in individuals with ASD (Dawson et al. 2004). Social Awareness subscore is composed of 11 items. Some examples are item 15 'Able to understand the meaning of other people's tone of voice and facial, expressions', item 38 'Responds appropriately to mood changes in others', item 45 'Focuses his or her attention to where others are looking or listening', or item 52 'Knows when he or she is talking too loud or making too much noise.'

The *Autism Spectrum Questionnaire (AQ)* (Baron-Cohen et al. 2001) is a self-report questionnaire developed to quantify "autistic traits" in adults with normal intelligence. It consists of 50 theoretically-derived statements depicting personal views, habits, and preferences pertinent to the unique profile of ASD. Each statement is rated on a four-point scale, with answer categories 'definitely agree,' 'slightly agree,' 'slightly disagree' and 'definitely disagree.' The former two are scored '1', and the latter two are '0', leading to the total score of the AQ ranges from 0 to 50 where a higher score depicts the autistic end of the continuum. The cutoff point suggested by Baron-Cohen et al. (2001) is 32, for 80% of ASD individuals scored higher than that, while 2% of TD individuals scored lower than that. In our sample, eight participants of the ASD group scored under 32, whereas none in the TD group scored above 32. The present study applied a new factor structure proposed by a recent study in 4192 Taiwanese parents (1208 with ASD children and 2984 with TD children) with favorable psychometric properties (Lau et al. 2013). Subscales of this new AQ Chinese model were

statistically and semantically coherent, including five subscales: Socialness, Mindreading, Patterns Preoccupation (i.e. preference for patterns, such as being fascinated by dates and numbers), Attention to Details and Attention Switching.

ERP Paradigms

Experimental Procedures

Audiometry testing was used to exclude subjects who could not detect 40-dB sound pressure level tones at 500, 1000, and 6000 Hz presented to either ear. No one was excluded after audiometry testing. All the participants did not smoke (Olincy and Martin 2005) and did not take medications 1 day before the procedure of ERP. They were asked to lie down in the supine position in a comfortable recliner in a sound attenuating, electrically shielded booth and instructed to relax with his/her eyes open and to focus on a cartoon running with no sound on the video monitor. Auditory tones were presented to the subjects binaurally via foam insert earphones during the oddball paradigm. The oddball paradigm for approximately 30-min length was given with standard (80%, 1000 Hz, 50 millisecond (ms) duration), duration deviant (10%, 1000 Hz, 100 ms duration), and frequency deviant (10%, 1200 Hz, 50 ms duration), tones presented in pseudorandom order. The cartoon soundtrack was turned off throughout the paradigms and was replaced by the experimental auditory stimuli which were presented at a fixed 500-msec onset-to-onset asynchrony according to the MMN guidelines (Duncan et al. 2009).

The EEG signals were recorded with a Quik-Cap from 32 scalp locations (Compumedics Neuroscan, El Paso, TX, USA). The auditory stimuli were generated by a Neuroscan STIM system, and data were recorded on a Neuroscan ACQUIRE system (Compumedics Neuroscan, El Paso, TX, USA). Stimuli were digitized at a rate of 1 kHz, with an on-line band-pass filter at 0.5–100 Hz, without 60-Hz notch filter applied as suggested by previous studies (Light et al. 2010; Picton et al. 2000). Electrodes placed at the tip of the nose and at Fpz (over the forehead) served as the reference and ground respectively (Duncan et al. 2009). Four additional electrodes were located above and below the left eye and at the outer canthi of both eyes to monitor blinks and eye movements. Electrode impedances were kept below 5 kΩ prior to recording.

On-line averaging was used to monitor the number of trials free from gross artifacts (defined as activities exceeding ± 100 μV in the -100 to 500 ms time window following the stimuli). The session continued until a minimum of 225 artifact-free deviant trials had been collected on line. In average, there were around 2000 trials in total for each subject, with 200 trials of duration deviant and 200 trials of frequency deviant. The ASD group spent an average of 33.8 ± 5.6 min that was not statistically different from the TD group (33.0 ± 4.7 min, $p = 0.50$).

Data Processing

All data were processed using Neuroscan Edit 4.3 software (Compumedics Neuroscan, El Paso, TX USA) by researchers who were blind to the subject's group (Boutros 2008). Semi-automated procedures using the Tool Command batch processing Language (TCL), began with EOG artifact reduction through a built-in pattern-recognition algorithm (Semlitsch et al. 1986). For MMN and P3a analysis, each subject's continuous data after EOG artifact reduction were then epoched 100 ms pre-stimulus to 500 ms post-stimulus. Following linear detrending and baseline correction to the average pre-stimulus interval, all epochs containing amplitudes exceeding ± 50 μV were automatically rejected (Wynn et al. 2010). EEG responses to standard and deviant stimuli were separately averaged to create a standard ERP and a deviant ERP, and both were low-pass filtered at 20 Hz (0-phase shift and 24-dB/octave roll-off) to remove any residual high-frequency artifacts. MMN and P3a waveforms were generated by subtracting the standard ERP from the deviant ERP. MMN and P3a were identified from 100 to 200 ms and 220 to 300 ms at the Fz electrode (Light et al. 2010; Michie et al. 2002; Wynn et al. 2010) where the maximal waves can be recorded. Data at Fcz and Cz were also presented as supplementary information. The peak amplitude and its latency were collected. All the parameters analyzed were summarized in Supplementary Table 1.

Statistical Analysis

Statistical analysis was conducted using SAS program 9.2 (SAS Institute Inc, Cary NC, USA). The comparison of the subscores of SP, SRS, and AQ, and ERP parameters between the ASD and TD groups were examined by the non-parametric Wilcoxon rank-sum test (two-sided, normal approximation), considering that non-parametric method is relatively robust if sample size is small or if the outliers exist (e.g., fP3a peak amplitude). The significant ERP parameter (dP3a latency) was compared again in the full-scale IQ-matched subsample (ASD, $n = 31$; TD, $n = 35$) with the adjustment of sex and age. The relationship between dP3a latency and social awareness deficits was tested by Spearman's correlation test (ρ) in each group and the whole sample. The correlations between ERP parameters and age and full-scale IQ were also examined by the Spearman's correlation test.

To explore the sensory correlates among the four sensory subscores, model selections containing sex, age and the sensory subscores (i.e., Low Registration, Sensation Seeking, Sensory Sensitivity, and Sensation Avoiding) were

performed in the ASD, TD separately, and the whole sample, by a stepwise selection method with $p < 0.10$ entry and $p < 0.05$ staying in the model.

To identify the specific autistic symptoms correlated with P3a amplitude and latency, we included sex, age, and all autistic symptom subscores as independent variables and P3a amplitude and latency as dependent variables in the multivariate regression models.

To find the significant ERP parameters which distinguish ASD from TD, we conducted the stepwise selection method in the logistic regression model. We combined the significant ERP parameters and the sensory subscores to predict the ASD diagnosis. The efficiency of the predictive model was estimated by the area under the receiver operating characteristic curve (AUC). In general, $0.7 \leq AUC < 0.8$ suggests acceptable discrimination; $0.8 \leq AUC < 0.9$ and $AUC \geq 0.9$ suggest excellent and outstanding discrimination, respectively. The statistical significance level was set at $p < 0.05$ level.

Results

The Comparison on Autistic Symptoms and Sensory Symptoms

Compared to the TD group, ASD participants scored higher in the Stereotyped Behaviors/Interest, Social Awareness, and Social Emotion problem of the SRS, as well as the Attention to Details and Attention Switching Difficulty subscores of the AQ (Table 1). As for sensory symptoms, ASD participants had significantly higher subscores on the Low Registration, Sensory Sensitivity and Sensation Avoiding but lower subscores on the Sensation Seeking as compared to TD participants (Table 2).

ERP Analysis

There were no significant group differences on MMN peak latency or peak amplitude (Fig. 1; Table 2). Whereas, ASD participants showed significantly shorter peak latency on dP3a (Fig. 1; Table 2). The results at Fcz and Cz were similar (Supplementary Table 2).

Age was positively correlated with dP3a (correlation coefficient $\rho = 0.45$, $p = 0.005$) and fP3a amplitudes ($\rho = 0.50$, $p = 0.002$) while negatively correlated with fP3a latency ($\rho = -0.33$, $p = 0.043$) only in the ASD group, but not in the TD

Table 2 The comparison of sensory profile and ERP parameters between the autism spectrum disorder (ASD) and typically-developing (TD) groups

	ASD (n = 37)		TD (n = 35)			
	Mean	SD	Mean	SD	Z	p
Sensory Profile						
Low registration	39.6	10.8	34.5	6.0	−2.98	0.003
Sensation seeking	38.0	8.1	46.0	7.0	4.12	< 0.0001
Sensory sensitivity	43.0	12.5	37.2	7.1	−2.81	0.005
Sensation avoiding	44.2	11.0	38.6	6.0	−2.80	0.005
MMN parameters						
dMMN peak latency	163.2	27.63	163.0	28.4	0.19	0.848
dMMN peak amplitude	−1.88	0.92	−1.79	0.96	0.37	0.710
fMMN peak latency	127.8	22.1	124.2	19.8	−0.87	0.382
fMMN peak amplitude	−1.47	0.84	−1.29	0.72	0.94	0.350
P3a parameters						
dP3a peak latency	259.2	13.6	268.7	17.6	2.48	0.013
dP3a peak amplitude	3.02	1.64	3.14	1.16	0.99	0.325
fP3a peak latency	251.1	36.5	239.9	18.9	−1.00	0.319
fP3a peak amplitude	1.51	0.86	1.38	0.73	−0.78	0.437

The comparisons were done by Wilcoxon two-sample test (two-sided, normal approximation). The subscores of Sensory Profile and ERP parameters were all raw scores. According to Tseng and Chen (2009), the means of Sensory Profile subscores in TD group were all within 1 S.D. of the norm, while the means of the ASD group were 1 S.D. higher or lower (i.e. Sensation seeking) from the mean of the norm

dMMN MMN in duration paradigm, *fMMN* MMN in frequency paradigm, *dP3a* P3a in duration paradigm, *fP3a* P3a in frequency paradigm

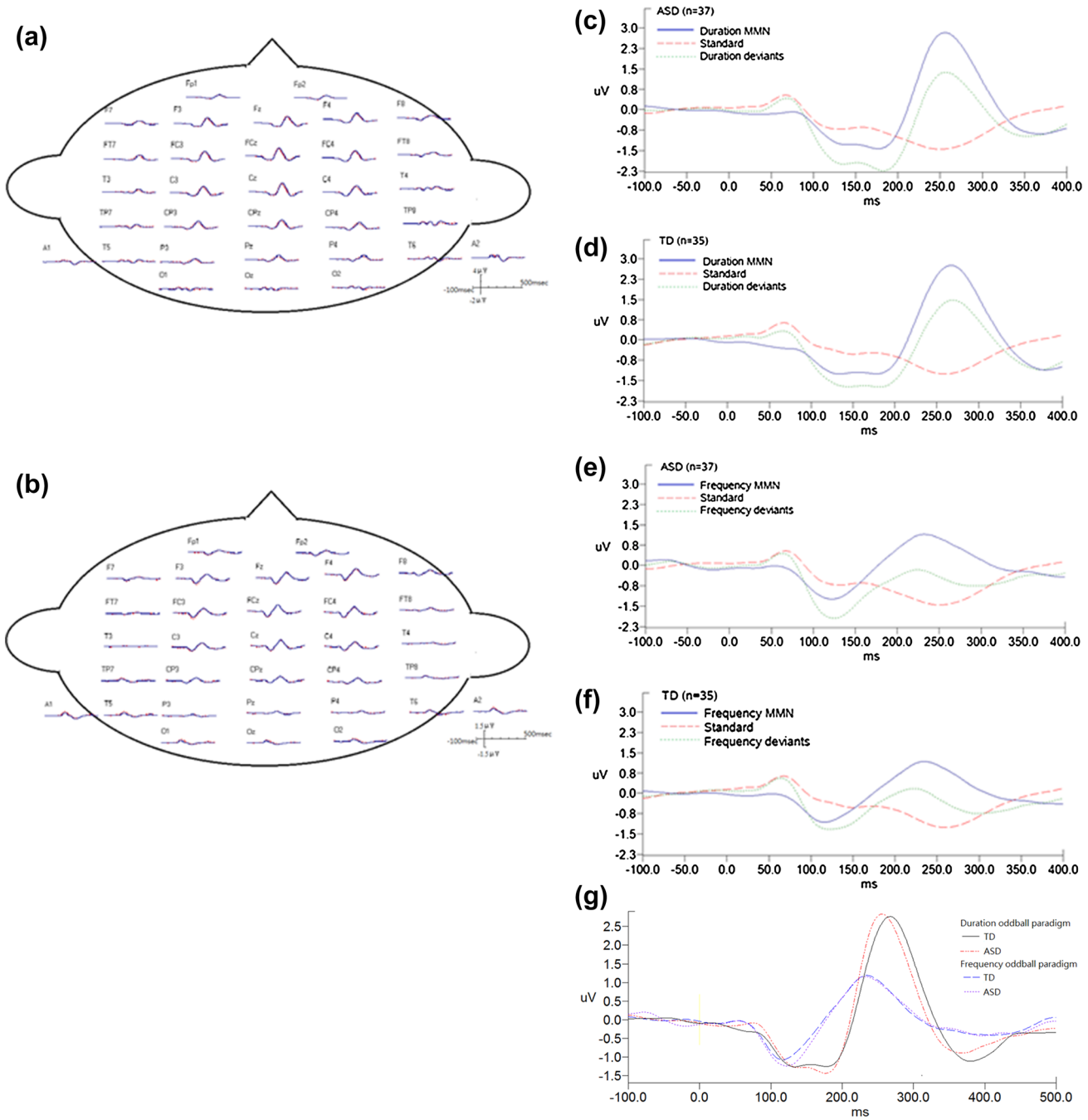

Fig. 1 **a/b** Grand average waveforms at each electrode for ASD (red dotted line; n = 37) and TD participants (blue line; n = 35) in **a** duration oddball paradigm and **b** frequency oddball paradigm. Because of the orientation of MMN/P3a generators, the waves reverse in polarity between frontal midline electrode and the mastoid electrodes. Waveforms of duration oddball paradigm were shown in **c** ASD and **d** TD, while those of frequency oddball paradigm were shown in **e** ASD and **f** TD. The waveforms of MMN/P3a (blue solid line) derived by substracting deviant stimuli (green dotted line) from standard stimuli (red dashed line). **g** MMN and P3a difference waves in an oddball paradigm with duration deviant and frequency deviant stimuli from the Fz electrode: the downwards waves (around 75–200 ms) were MMN and the upwards waves (around 200–300 ms) were P3a

group (Supplementary Table 3). All the MMN parameters were not associated with age. Both MMN and P3a parameters were not associated with full-scale IQ in the ASD or TD group except a negative association noted between full-scale IQ and fP3a peak latency ($\beta = -0.86 \pm 0.37$, $F_{(1,27)} = 5.48$, $p = 0.027$) in ASD. The significant difference of dP3a peak latency between the ASD and TD groups remained in the IQ-matched subsample ($F_{(3,62)} = 5.87$, $p = 0.018$).

The Sensory and Clinical Correlates of P3a Parameters

We therefore identified sensory correlates for P3a parameters by model selection. Among the four sensory subscores, the Sensation Avoiding subscore remained in the models to predict fP3a peak latency in the whole sample ($\beta = -0.68 \pm 0.34$, $F_{(1,68)} = 4.00$, $p = 0.049$) and in the ASD group ($\beta = -1.18 \pm 0.47$, $F_{(1,33)} = 6.30$, $p = 0.017$), and also in the models to predict fP3a amplitude in the whole sample ($\beta = 0.02 \pm 0.01$, $F_{(1,68)} = 5.07$, $p = 0.028$) and in the TD group ($\beta = -0.05 \pm 0.02$, $F_{(1,70)} = 6.96$, $p = 0.013$). Spearman's correlation analyses revealed similar results. The Sensation Avoiding subscore was negatively correlated with fP3a peak latency in the ASD group ($\rho = -0.50$, $p = 0.003$), but was positively correlated with fP3a peak amplitude in the TD group ($\rho = 0.39$, $p = 0.019$) (Fig. 2).

To examine the clinical correlates for P3a parameters, we performed model selection containing the autistic symptom subscores. Among the autistic symptom subscores, the Social Awareness subscore remained in the model to predict dP3a latency in the whole sample ($\beta = -0.72 \pm 0.28$, $F_{(1,70)} = 6.73$, $p = 0.012$), while the Patterns Preoccupation subscore remained in the model to predict fP3a peak amplitude in the whole sample ($\beta = 0.08 \pm 0.03$, $F = 5.64$, $p = 0.021$) and in the TD group ($\beta = 0.16 \pm 0.053$, $F_{(1,33)} = 11.80$, $p = 0.002$). Meanwhile, the Attention to Details subscore was associated with fP3a peak latency only in the ASD group ($\beta = -7.81 \pm 2.15$, $F_{(1,29)} = 13.17$, $p = 0.001$), while Attention Switching subscore ($\beta = -3.65 \pm 1.47$, $F_{(2.32)} = 6.14$, $p = 0.0187$) together with Social Emotion subscore ($\beta = 3.49 \pm 1.03$, $F_{(2.32)} = 11.45$, $p = 0.019$) stayed in the model to predict dP3a latency only in the TD group. dP3a amplitude was not associated with any of autistic symptom subscores.

dP3a Latency versus Social Awareness Deficits

Focusing on the relationship between dP3a latency and social awareness deficits, the Social Awareness subscores were negatively correlated with dP3a latency in the ASD group ($\rho = -0.37$, $p = 0.039$) and in the whole sample ($\rho = -0.36$, $p = 0.002$), but not in the TD group ($p = 0.985$) (Fig. 3). When the two ASD outliers and one TD outlier with large dP3a latency were deleted, the linear regression analysis controlling for sex and age revealed similar results (ASD: $t = -2.10$, $p = 0.044$; whole sample: $t = -2.89$, $p = 0.005$).

Predictive Models for the Diagnosis of ASD

Through stepwise selection model among the eight ERP parameters, the two latency parameters of P3a (dP3a and fP3a) were selected in the model to predict diagnosis status (AUC = 0.733, acceptable discrimination). Since the directions of the two parameters are the opposite (dP3a latency OR 1.014–1.096 [95% Wald confidence limits], $p = 0.007$; fP3a latency OR 0.954–1.000, $p = 0.048$), we created a combined indicator of 'dP3a latency/fP3a latency' ratio and found that the ratio was significantly different between the ASD and TD groups ($Z = -2.80$, $p = 0.005$). This ratio was correlated with several autistic symptom subscores, i.e. Social Communication, Stereotyped Behaviors/Interest, Social Awareness deficits, Social Emotion and total scores of the SRS, as well as Socialness and Mindreading and total scores of the AQ ($\rho = 0.253$–0.382, $p < 0.05$).

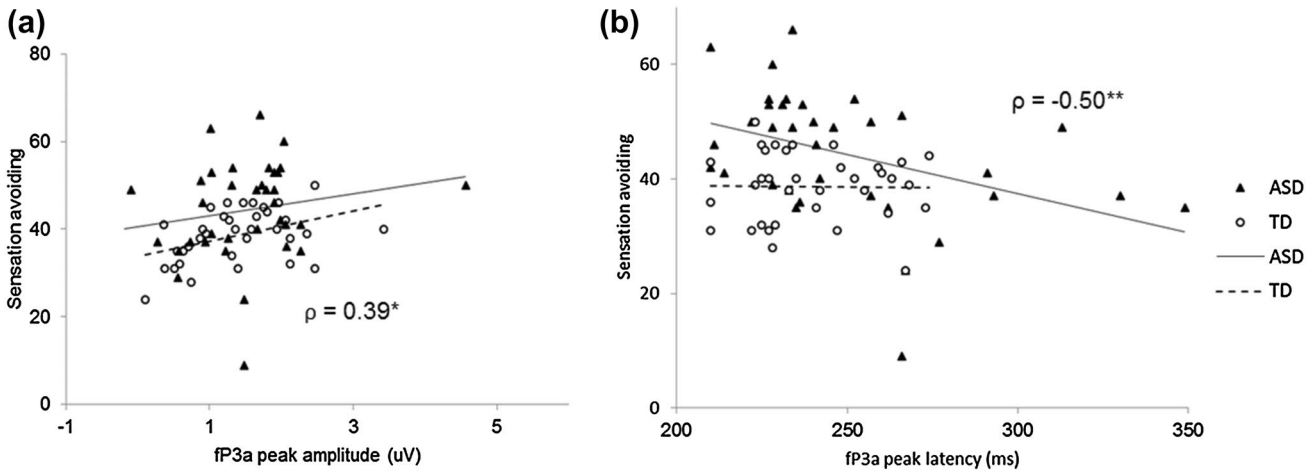

Fig. 2 Spearman's correlation (correlation coefficient, ρ) between Sensation avoiding subscores and frequency P3a (fP3a) parameters: **a** Positive correlation with fP3a peak amplitude in typically-developing participants; **b** Negative correlation with fP3a peak latency in participants with autism spectrum disorder. (*$p < 0.05$, **$p < 0.005$)

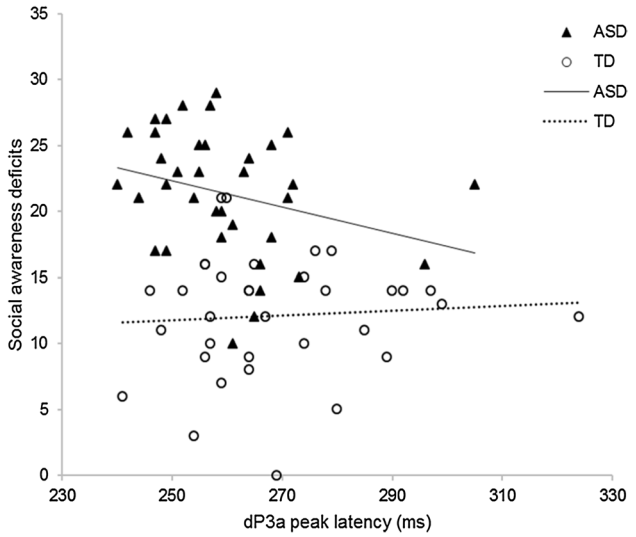

Fig. 3 The Social Awareness subscores were negatively correlated with duration P3a latency (dP3a) in individuals with autism spectrum disorder (ASD: Spearman's correlation coefficient: $\rho = -0.37$, $p = 0.039$) but not in typically-developing controls (TD: $\rho = -0.00$, $p = 0.985$). When the two ASD outliers and one TD outlier with large dP3a latency were deleted, the results were similar by using linear regression controlling for sex and age (ASD: $t = -2.10$, $p = 0.044$; combined ASD and TD: $t = -2.89$, $p = 0.005$)

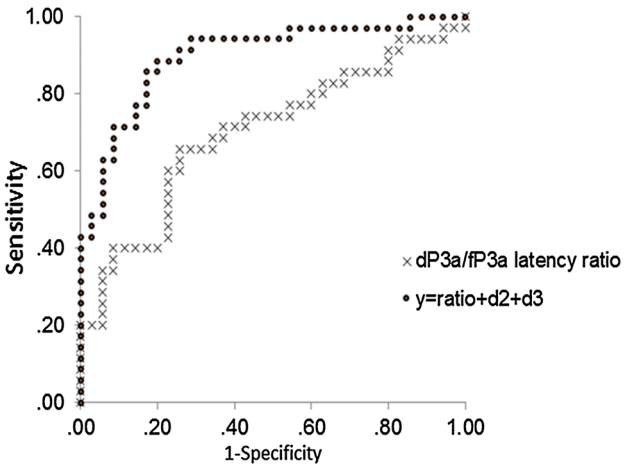

Fig. 4 The ROC curve for predictive model: using the ratio of duration P3a (dP3a) latency and frequency P3a (fP3a) latency and the subscores of Sensation Seeking (d2) and Sensory Sensitivity (d3) to predict diagnosis status (autism spectrum disorder). The two latency parameters of P3a (dP3a and fP3a) together showed acceptable discrimination (AUC = 0.733); the 'dP3a latency/fP3a latency' ratio combined with Sensation Seeking (d2) and Sensory Sensitivity (d3) were excellent in discriminating ASD from TD (AUC = 0.899)

After the Bonferroni correction, this ratio was still correlated with Social Awareness deficits ($p = 0.009$) and Socialness ($p = 0.028$).

Using the ratio (dP3a latency/fP3a latency) to predict the ASD diagnosis, we found dP3a latency/fP3a latency ratio could only predict the diagnosis status with AUC 0.693. If we included the four SP subscores together with the ratio for model selection, we found the ratio (OR < 0.001–0.055, $p = 0.008$) combined with Sensation Seeking (OR 1.100–1.373, $p = 0.0003$) and Sensory Sensitivity (OR 0.782–0.932, $p = 0.0004$) could predict the ASD diagnosis with AUC 0.899, suggesting excellent discriminative validity (Fig. 4). Besides, this model explained 22.8% (Attention to Details)–55.2% (Socialness) variances (R^2) for autistic symptom subscores.

Discussion

The current study is one of few studies investigating the behavioral correlates of ERP parameters in terms of sensory symptoms and autistic symptoms. The major findings are that individuals with ASD had greater sensory symptoms and a shorter dP3a peak latency compared to the TD group but did not show abnormal MMN or P3a amplitude, and that the association between a shorter dP3a peak latency and social awareness deficits was noted in the ASD group. We also found specific correlates for fP3a responses for the ASD and TD groups. The fP3a amplitude was positively correlated with sensation avoiding and patterns preoccupation in the TD group; the fP3a latency was negatively correlated with sensation avoiding and attention to details in the ASD group. Our findings provided evidence of perceptual disturbance as measured by P3a in adolescents and young adults with ASD and depicted behavioral correlates and clinical implication of P3a parameters.

Consistent with recent studies (Crane et al. 2009; Mayer 2017), our findings support that adolescents and adults with ASD had greater sensory symptoms compared to the TD controls, showing a pattern of greater symptoms in low registration, sensory sensitivity, sensation avoiding, while less symptoms in sensation seeking (Crane et al. 2009; Mayer 2017). This pattern is in line with the findings in childhood that children with Asperger syndrome displayed greater sensory symptoms than controls except for lower sensory seeking behaviors (Dunn et al. 2002), suggesting that sensory profile in youth with ASD may persist into adulthood.

To our knowledge, although the study of Clery et al. (2013) has suggested a shorter P3a latency in a visual oddball paradigm, this study is the first to report on latency difference of P3a to auditory oddballs in ASD individuals. The shorter latency of dP3a in the ASD group may reflect an earlier cortical response toward auditory stimuli. Interestingly, the shorter latency of dP3a indeed correlated with social awareness deficits found in the ASD group and the whole sample, suggesting that the earlier orienting reflected greater impairment of social awareness. This correlation provided further evidence to show that P3a is not only related to

attention orienting but its latency may also have implications on social awareness. An earlier orienting to subtle changes in the environment may distract or preclude the individuals from processing social stimuli appropriately which are often complex and rapidly changing (Dawson et al. 2004), particularly for ASD individuals who have a bias toward low-level information processing (Lepistö et al. 2005). As P3a has been proposed as an indicator of social orienting (Lepistö et al. 2005) based on the studies that P3a deficits were more significant in speech sound than non-speech sound (Ceponiene et al. 2003; Lepistö et al. 2005), our findings of a shorter dP3a latency in the ASD group and its relationship to social awareness deficits support impaired social orienting in this disorder (Dawson et al. 2004; Mundy and Neal 2001). Notably, we found that among P3a parameters, only the dP3a latency did not change with both age and full-scale IQ in the ASD group, suggesting its potential value as a stable marker. These novel findings warrant validation.

Our results did not display any statistical difference on the MMN or P3a amplitudes between the ASD group and the TD group. Although previous studies in children with ASD have shown a higher P3a amplitude toward frequency change (Gomot et al. 2011) or a smaller or absent P3a toward speech sound (Lepistö et al. 2005, 2006), two studies in adults with Asperger's disorder (Iwanami et al. 2014; Lepistö et al. 2007) indicated an enhanced P3a for changes in non-speech sounds compared to controls (Iwanami et al. 2014; Lepistö et al. 2007). Our findings, based on a larger sample of adolescents and young adults with ASD and TD, suggest no difference in P3a amplitudes, consistent with a recent study in adults with this disorder (Karhson and Golob 2016) and a meta-analysis across age groups (Cui et al. 2016). We found that dP3a and fP3a amplitudes increased with age while fP3a latency decreased with age in the ASD group and that all three parameters were not different between ASD and TD individuals. These findings might imply that the P3a responses of ASD individuals became closer to their TD counterparts when they grew up from late adolescence to adulthood. In other words, ASD individuals might respond better in orienting to new events when they were adults. Our findings, together with Lepistö et al's work that shows a trend of increasing P3a amplitude and shortening latency from adolescence (Lepistö et al. 2005, 2006) to adulthood (Lepistö et al. 2007), might support a developmental trajectory on normalization of impaired attention orienting (P3a deficits) through childhood to adulthood. The developmental changes of P3a needs further investigations.

Several factors may explain the inconsistent findings in MMN amplitudes across studies, including differences in age population, IQ profiles, and oddball paradigms (Cui et al. 2016). First of all, consistent with a previous report (Ferri et al. 2003), MMN parameters were not associated with age in either ASD or TD groups, suggesting that MMN parameters are relatively stable traits in ASD as well as TD individuals from adolescence to adulthood. Previous studies in children with ASD showed a shorter latency and larger amplitude to frequency change (age range 5–15) compared to age-matched TD youth (Ferri et al. 2003; Gomot et al. 2002, 2006, 2011), while another study reported a diminished MMN amplitude when detecting duration change (Lepistö et al. 2005). Our study added new evidence for the age group 15–30, implying that brain response (hyper- or hypo-responsiveness) to change detection in ASD individuals could become not only similar to TD individuals before they get into adulthood but also maintain stable during early adulthood. These findings are also in accordance with our clinical observations that the auditory sensitivity in ASD adults are generally not as much as that in their childhood, reflecting a process of adaptation. Since evidence suggests that frontotemporal interactions are crucial to the generation of MMN during auditory deviant processing (Choi et al. 2013; Hsiao et al. 2010), it is intriguing to know whether the normalization in MMN amplitudes from childhood to adulthood reflect the normalization of early hyperconnectivity in the ASD brains. Second, MMN abnormalities have been shown to depend on cognitive ability (Ceponiene et al. 2003) for that ASD individuals with normal intelligence are not different from their counterparts. In this sense, our finding of no MMN abnormality may also be attributable to the normal IQ of the sample (full-scale IQ = 99.1). Whether the MMN abnormality in ASD individuals with normal IQ are more likely to be normalized with age than their counterparts is another focus of interest. Third, task-sensitivity effects (i.e., a more deviant stimulus may arouse a larger MMN amplitude) may also explain the controversial results across studies, such as the high pitch vs. low pitch contrast as 125:113 Hz in Lepistö et al's study (2007) and 1200:1000 Hz in ours. These discordant results await longitudinal studies using the appropriate contrast of stimuli to clarify.

Our results suggest different behavioral correlates for P3a between the ASD and TD groups. The fP3a amplitude was correlated with sensation avoiding in the TD group, suggesting that P3a may not only represent attention orienting (Escera et al. 2000), but also be associated with sensory characteristics in daily life. More interestingly, TD participants with higher fP3a amplitudes also displayed preoccupation on the patterns, corresponding to the alertness towards changes in the surroundings (Lepistö et al. 2005). Our findings provide evidence for the behavioral correlates of fP3a amplitudes in the TD brain that have not yet been established, implying that individuals with higher attention orienting to deviants may tend to avoid sensation and are more sensitive to the patterns in daily life. Notably, these associations were not found in ASD participants. Donkers et al. (2013) reported that attenuated P3a amplitude was associated with greater sensory seeking in specific range of

P1 responses. It is unclear whether the correlations found in the TD group can still be observed in the ASD group within a specific range of frequency change. Attention orienting neural responses to stimuli may underlie selective sensory features via complex mechanisms (Donkers et al. 2013), the roles of brain connectivity (changed from hyper- to hypo-connectivity in ASD individuals) and interventions (e.g., sensory integration) in explaining the disruption of correlations in ASD young adults wait to be examined. Instead, P3a latency were correlated with autistic symptoms in the ASD group, with a shorter latency associated with attention to details (fP3a) and social awareness deficits (dP3a), supporting that advanced attention-orienting neural responses to stimuli (Mantini et al. 2009) may underlie clinical features within ASD population (Donkers et al. 2013). These exploratory findings, if being replicated, imply that P3a parameters might have a possible role as neurophysiological markers which correlate with clinical severity of autistic and sensory symptoms.

Combining the latency ratio of dP3a and fP3a oddball paradigms, together with self-report sensory seeking and sensory sensitivity, the ASD group could be differentiated from the TD group without the information of social or communication symptoms, implying its possible role to assist the clinical diagnosis in adults with ASD. This finding suggests that sensory symptoms and P3a latency deviations might be trait markers for ASD, for their persistence into adulthood and the association with autistic core symptoms. However, this novel model needs to be validated in independent samples to test its specificity to ASD diagnosis.

Our findings suggest an inter-relationship between perceptual disturbances and autistic core deficits. P3a reflects an alerting process in the frontal lobe when involuntary attention is redirected to unexpected events (Yamaguchi and Knight 1991). The major generator is localized within the frontal cortex and anterior cingulate cortex (ACC) (Wronka et al. 2012), both of which have shown abnormal activation and connectivity in ASD (Agam et al. 2010; Delmonte et al. 2013). Research has postulated that ACC exerts top-down attentional modulation of sensory processing (Crottaz-Herbette and Menon 2006) and may involve socio-cognitive deficits (i.e., joint attention and social cognition) in autism (Mundy 2003). If ACC dysregulation mediates the latency of P3a response and daily behaviors (such as social awareness deficits, attention to details and sensation avoiding) warrants further investigation. In addition, based on a previous finding that brain hyperconnectivity predicted social impairment in children with ASD (Supekar et al. 2013), the aberrant functional connectivity may underlie social deficits. The relationship between functional connectivity and behaviors may provide a framework to understand the complex behavioral and electrophysiological phenotypes of ASD. Whether functional connectivity between sensory and social regions moderates the relationship between P3a latency and social awareness needs more studies.

This study has several limitations. First, male predominance and normal IQ of our sample may limit the generalizability of our results to the whole ASD population. Although a positive correlation between the P3a amplitude and intelligence has been reported (Wronka et al. 2013), we did not find correlations between IQ and P3a parameters except for fP3a latency (in the ASD group). Hence we did not control for IQ in the group comparison. Instead, we compared MMN and P3a parameters again in the IQ-matched subsample, and the results were similar. Second, the autistic symptoms and sensory symptoms are self-report. Although normal IQ of our sample may reflect a less biased report because of a better comprehension, the correlation findings for the self-report symptoms still need to be validated. Future studies may consider to include caregiver-report autistic and sensory symptoms, or adopt objective tasks to quantify sensory and social behaviors. In addition, the age effect should be cautiously interpreted, considering the limited age range of the sample. The developmental effect on P3a parameters warrants longitudinal studies with a wider age range covering the adolescence and adulthood.

As one of the first studies to investigate both P3a and MMN on the standardized paradigm and the behavioral correlates in a larger ASD adolescent and adult sample, our findings have several implications. Adolescents and young adults with ASD did not show abnormal amplitude in MMN or P3a but revealed shorter dP3a response that was correlated with social awareness deficit. P3a latency might serve as a potential neurophysiological biomarker for ASD where a shorter latency of P3a might reflect more severe autistic symptoms (i.e., social awareness deficits and attention to details) and sensation avoiding on self-report measures. Meanwhile, the ratio of P3a latency and reported sensory symptoms together might possibly differentiate the ASD group from the TD group, suggesting the significance of diagnostic value combining the subjective perceptual disturbance and the electrophysiological marker. These findings warrant validation in other independent and larger samples in order to examine the specificity and sensitivity of P3a as a biomarker for sensory profiles of ASD. Also, whether behavior treatment influences P3a response is worth to be examined in the future.

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Author Contributions YC conceived of the study, participated in its design and coordination, collected the sample, analyzed the data and drafted the manuscript; MH performed the event-related potentials

measurement, participated in the data analysis and interpretation; SG participated in the design and coordination of the study, confirmed the clinical diagnosis, supervised the statistical analysis and data interpretation, and did rigorous revision on the manuscript. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Conflict of interest The authors declare no competing financial interests.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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